I. Remarks

After entry of the amendment, claims 93-120 and 144-151 are pending.

Claim 120 has been editorially amended, rendering the rejection under 35 USC § 112, second paragraph, moot.

New claims 144-151 are supported by the originally filed claims and the specification at, for example, Examples 2-7.

Method claims 121-143 have been canceled without prejudice in view of the restriction requirement. Applicant reserves the right to file a divisional application directed to this non-elected subject matter.

No issues of new matter should arise and entry of the amendment is respectfully requested.

II. Rejection under 35 U.S.C. § 112, First Paragraph: Written Description

Claims 93-97, 99, 102-110, 112, 115-120 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Applicant respectfully traverses the rejection. An adequate written description requires that the specification convey to one having ordinary skill in the art that applicants were in possession of the claimed invention. Applicant respectfully submits that the specification adequately describes the claimed invention.

As the U.S. Patent Office (PTO) acknowledges, the claims are not drawn to cancer antigens. If the claims and specification are not drawn to cancer antigens, there is absolutely no basis for the PTO to reject the claims as lacking a written description for cancer antigens. Moreover, cancer antigens and methods for isolating them were well known in the art at the time the application was filed. *See*, for example, Stern et al, *Cancer Vaccines and Immunotherapy*, pages 1-18 and 195-206, Cambridge University Press (2000), attached hereto as Exhibit A; Kast, *Peptide-Based Cancer Vaccines*, pages 1-16, Eurekah.com, (2000), attached hereto as Exhibit B. It is not necessary to include information in an application that was well known to one skilled in the art at the time the application was filed.

At the time the application was filed, it was well known that one skilled in the art could produce monoclonal antibodies that bind to antigens expressed by cancer cells. In support thereof, Applicant refers to "Monoclonal Antibody Production," A Report of the Committee on

Methods of Producing Monoclonal Antibodies, Institute for Laboratory Animal Research, National Research Council, National Academy Press, Washington, DC, 1999 (attached as Exhibit C).

Scientific literature and the patent literature describe countless monoclonal antibodies that bind with antigens expressed by cancer cells. For example, U.S. Patent No. 5,242,824 issued September 7, 1993 (attached as Exhibit D), at column 1, lines 33-45, teaches:

> **Monoclonal antibodies reactive with carcinoma-associated antigens are known** [see, e.g., L. D. Papsidero, "Recent Progress in the Immunological Monitoring of Carcinomas Using Monoclonal Antibodies, Semin. Surg. Oncol., 1 (No. 4), pp. 171-81 (1985); J. Schlom et al., "Potential of Human Carcinomas", Important Adv. Oncol., 1985, pp. 170-192; W. H. Allum et al., "Monoclonal Antibodies in the Diagnosis and Treatment of Malignant Conditions", Surg. Ann., 18, pp. 41-64 (1986); and A. N. Houghton et al., "Monoclonal Antibodies: Potential Applications to the Treatment of Cancer", Semin. Oncol., 13 (No. 2), pp. 165-179 (1986)].

Applicant draws the PTO's attention to US Patent No. 5,208,020 issued May 4, 1993,[1] where claim 1 recites:

> 1. A cytotoxic agent comprising one or more maytansinoids linked to a monoclonal antibody or fragment thereof via a disulfide bridge at the C-3, -14, -15, or -20 position of said maytansinoids and wherein said monoclonal antibody or fragment thereof is selective for tumor cell antigens.

This claim is not limited to particular monoclonal antibodies because – in 1993 – monoclonal antibodies selective for tumor cell antigens were well known in the art.

Monoclonal antibodies that bind to antigens expressed internally by cancer cells, and their ability to be used as immunoconjugates, were also well known in the art at the time the application was filed. As one example, U.S. Patent No. 5,242,824 issued September 7, 1993 (attached as Exhibit D), at column 3, lines 36-54, teaches:

> The present invention provides such an internalizing antibody that is highly selective for a range of human carcinomas. More specifically, the novel antibody of the invention, illustrated by BR64, is a monoclonal antibody that binds to a glycolipid cell membrane antigen found on the surface of human carcinoma cells. The antibody is highly specific for

[1] US Patent No. 5,208,020 was cited in an Information Disclosure Statement in this application.

> carcinoma cells, such as those derived from breast, lung, colon, and ovarian carcinomas, showing only a low degree of reactivity with certain normal human cells and no detectable reactivity with other types of tumors, such as lymphomas, sarcomas or melanomas. In addition, the antibody of the invention internalizes within the carcinoma cells to which it binds and thus is of particular use for therapeutic applications, for example, as the antibody component of antibody-drug and antibody-toxin conjugates where internalization of the conjugate is favored.

The pending claims are drawn, *inter alia*, to monoclonal antibodies that bind to an antigen expressed by a cancer cell. The antigen can be expressed externally or internally because monoclonal antibodies that bind to antigens expressed by cancer cells were well known in the art at the time the invention was made.

The PTO has no basis for this rejection in view of the extensive knowledge in the art about monoclonal antibodies that bind to antigens express by cancer cells. The Applicant has provided working examples of two monoclonal antibodies that target cancer cells, i.e., humanized N901 and humanized C242. The specification also lists numerous other monoclonal antibodies that target cancer cells, including J5, anti-B4, NKH-1, Leu-7, anti-Leu-7, S-L 3-5, S-L 4-20, S-L 11-14, TFS-4, MOC-1, MOC-21, MOC-31, MOC-32, MOC-52, 123A8, 123C3, UJ13A, B10/B12, SWA4, SWA20, SWA21, SWA22, SWA23, LAM-8, 534F8, 703D4704A1, SM1 (specification at page 17, lines 6-13; page 18, lines 3-22).

Again, monoclonal antibodies that target cancer cells were well known in the art at the time the application was filed. For example, numerous anti-cancer antibodies have been approved by the FDA and numerous anti-cancer antibodies are in human clinical trials. Exemplary anti-cancer antibodies include trastuzumab (HERCEPTIN® by Genentech); rituximab (RITUXAN® by Genentech); pertuzumab (OMNITARG® by Genentech); cetuximab (ERBITUX® by ImClone Systems Incorporated); IMC-1C11 (ImClone Systems Incorporated); tositumomab and iodine I^{131} tositumomab (BEXXAR® by Corixa Corporation); In^{111} ibirtumomab tiuxetan and Y^{90} ibirtumomab tiuxetan (ZEVALIN® by Biogen Idec); bivatuzumab mertansine, and the like.

Monoclonal antibodies that bind to antigens expressed by cancer cells are not new technology. This is a well established field and those skilled in the art have very high levels of knowledge. In view of the teachings in the specification and the knowledge in the art at the time

the application was filed, one skilled in the art would clearly recognize that the Applicant was in possession of the claimed invention.

This rejection is also inconsistent with, and contrary to, the teachings in the prior art references cited in the obviousness rejections in the Office Action, including, for example, Siegall, Schlom and Pegram.

For example, Siegall et al, *Proc. Annu. Meet Am. Assoc. Cancer Res.*, 38, A185 (1997) teaches an immunoconjugate comprising an monoclonal antibody, BR96 sFv, that is effective for treating cancer. With respect to BR96 sFv, Friedman et al, *Cancer Research*, 53(2):334-339 (1993) (attached as Exhibit F), teaches:

> Monomeric BR96 sFv-PE40 was found to be extremely cytotoxic against cancer cells displaying the BR96 antigen. The cytotoxicity of the fusion protein correlates directly with antigen density on the tumor cell lines tested. The breast carcinoma cell line MCF-7, which has the highest density of BR96 antigen, was the most sensitive to BR96 sFv-PE40, with a concentration producing 50% protein synthesis inhibition of 5 pM. BR96 sFv-PE40 was found to have a t1/2 in serum of 28.5 min in athymic mice, compared to that of the chemical conjugate, chiBR96-LysPE40, which was 54 min. These data indicate that the single-chain immunotoxin BR96 sFv-PE40 is a potent inhibitor of protein synthesis in target cell lines and may be an effective agent for the treatment of cancer.

This is yet another example of a monoclonal antibody that was well known in the art at the time the application was filed that effectively targets cancer cells.

As another example, Schlom, Monoclonal Antibodies: They're More and Less Than You Think (cited by the PTO) provides a representative list of more than 109 different monoclonal antibodies to human tumor antigens (Schlom at page 96, Table 6.1). One skilled in the art would appreciate that any of these antibodies could be used in the presently claimed invention.

As another example, Pegram et al, *Oncogene*, 18:2241-2251 (1999) teaches that HER-2/neu monoclonal antibodies effective against breast cancer were well known in the art at the time the application was filed. One skilled in the art would appreciate that any of these antibodies could be used in the presently claimed invention.

In view of the above, Applicant respectfully submit that claims 93-97, 99, 102-110, 112, 115-120 satisfy 35 USC § 112, first paragraph, and respectfully request that the rejection under 35 U.S.C. §112, first paragraph of these claims be withdrawn.

III. Rejection under 35 USC § 112, First Paragraph: New Matter

Claim 120 is rejected for broadening the scope of the invention as originally filed by introducing new matter into the application.

Applicants respectfully traverse the rejection because no new matter has been added to the application. The current specification is exactly the same as the specification that was filed September 29, 2000, and claim 120 is commensurate in scope with the originally filed application. For example, the specification at page 2, lines 4-6 states:

> The present invention is based on the discovery that the use of at least one chemotherapeutic agent and at least one immunoconjugate produces unexpectedly superior results in the treatment of cancer.

Claim 120 is commensurate in scope with the specification as originally filed at, for example, page 2, lines 4-6. The invention teaches that the combination of chemotherapeutic agent and immunoconjugate produces unexpectedly superior results, and the working examples support the teachings in the specification. Unexpectedly superior results is the same as synergistic results and is the same as greater than additive results. "Synergism" is defined as "cooperative action of discrete agencies such that the total effect is greater than the sum of the effects taken independently." *See* Webster's New Collegiate Dictionary, G&C Merriam Co., page 1174 (1981), attached as Exhibit G. No new matter has been added to the application. In view thereof, Applicants respectfully request that this rejection be withdrawn.

IV. First Rejection under 35 U.S.C. § 103 and Obviousness-Type Double Patenting Rejection

Claims 93-97, 99, 102-110, 112, 115-119 are rejected under 35 U.S.C. § 103(a) over Siegall et al, *Proc Annu Meet Am Assoc Cancer Res*, 38:A185 (1997) in view of Chari et al, *Cancer Research*, 52:127-131 (1992).

Claims 93-97, 99, 102-110, 112 and 115-119 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-12 of US Patent No. 5,208,020 in view of Siegall et al, *Proc. Annu. Meet Am. Assoc. Cancer Res.*, 38:A185 (1997) and Chari et al, *Cancer Research*, 52:127-131 (1992).

Applicant respectfully traverses the rejections and respectfully submits that the presently claimed invention is unobvious over the combination of cited references.

Siegall is wholly unrelated to the presently claimed invention. Siegall describes an immunoconjugate containing a monoclonal antibody bound to a truncated form of Pseudomonas exotoxin. *See* Friedman et al, *Cancer Research*, 53(2):334-339 (1993), attached hereto as Exhibit F. The PTO has not established any relationship between the immunoconjugate in Siegall, which contains a truncated form of Pseudomonas exotoxin, and the presently claimed immunoconjugate which comprises a maytansinoid.

The PTO asserts that "[o]ne of skill in the art would recognize that both PE40 and maytansin are protein toxins which would act catalytically within the cell, thus one of skill in the art would expect that a BR96-sFv-maytansinoid immunotoxin would have a similar therapeutic potential as the Br96-sFc-Pe40 immunotoxin."[2] The PTO's assertion is factually incorrect. PE40 is a catalytically active bacterial protein toxin that kills cells by ADP-ribosylation of elongation factor 2 (Pastan et al, *J. Biol. Chem.*, 264:15157-15160 (1989), attached as Exhibit H). Maytansine is an antibiotic originally isolated from an African shrub and is chemically an ansamacrolide or polyketide. (Kupchan et al, *J. Am. Chem. Soc.*, 94: 1354-1356 (1972), attached as Exhibit I). Maytansinoids are antimitotic agents that bind to the intracellular protein tubulin and inhibit its polymerization to form microtubules. The claimed maytansinoids are not enzymes (i.e., like PE40) nor do they act catalytically in any other fashion (i.e., like PE40). Accordingly, Siegall, which teaches immunoconjugates comprising PE40, is wholly unrelated to the presently claimed invention.

Because the basis for the PTO's rejections are factually incorrect, Siegall does not properly form a basis to reject the present claims. Without Siegall, the rejections cannot be maintained. Accordingly, the rejection under 35 USC § 103 and the obviousness type double patenting rejection must be withdrawn.

[2] Office Action dated February 5, 2004, at page 6.

V. Second and Third Rejections under 35 USC § 103

(Second Rejection): Claims 93-97, 99, 101-110, 112, 114-119 are rejected under 35 USC § 103 as being obvious over Liu, *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) in view of Iwasaki et al, *Yakugaku Zasshi*, 118:111-126 (1998) and Pegram et al, *Oncogene*, 18:2241-2251 (1999) and Watson et al, *Proc Annu Meet Am Assoc Cancer Res*, 37:A2997 (1996) and Schlom (Monoclonal Antibodies: They're More and Less Thank You Think, *Molecular Foundations of Oncology*, 1991, Ed. S. Broder, pp. 95-134).

(Third Rejection): Claims 93-98, 100-111, 113, 115-119 are rejected under 35 U.S.C. § 103(a) as being obvious over Guchelaar et al, *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) in view of Liu et al, *Proc Annu Meet Am Assoc Cancer Res*, 38:A190 (1997) and Lynch et al, *Journal of Clinical Oncology*, 15:723-734 (1997) and Liu *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) and Iwasaki et al, *Yakugaku Zasshi*, 118:111-126 (1998) and Pegram et al, Oncogene, 18:2241-2251 (1999).

Applicant respectfully traverses the rejections and respectfully submits that the presently claimed invention is unobvious over the combination of cited references. After summarizing and analyzing the references, the PTO concludes the second and third obviousness rejections with the following statement:

> Because the mechanisms of action of these two agents differ with respect to the molecular basis by which they induce an anti-mitotic effect, it is logical to suppose that the combination of the two agents might produce some additive effect.[3]

Contrary to this statement, the data in the specification demonstrates that the combination of the claimed immunoconjugate and chemotherapeutic agent produce synergistic (i.e., more than additive) effects. As admitted by the PTO, it would be logical to suppose that the two "might produce some additive effect." Accordingly, it would be completely unexpected that the two would produce more than an additive effect (i.e., a synergistic effect). This is Applicant's basis for overcoming the obviousness rejections.

The data in the specification shows that the presently claimed compositions/kits provide superior (i.e., greater than additive, synergistic) results that would be unexpected in view of the

[3] Office Action at page 9, lines 13-15 and page 11, lines 9-12.

teachings in the cited references and the statements made by the PTO.[4] For the Examiner's convenience, a summary of the data in the specification is shown below.

	Treatment Groups	Therapeutic agents	Results
Example 2	Control	Untreated	Tumors grew rapidly to a size of about 900 mm^3 by day 28 post-tumor inoculation
	Group 1	huN901-DM1	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 2	Paclitaxel	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 3	huN901-DM1 and paclitaxel	Tumors disappeared with complete regression lasting 58 days
Example 3	Control	Untreated	Tumors grew rapidly to a size of about 900 mm^3 by day 28 post-tumor inoculation
	Group 1	huN901-DM1	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 2	cisplatin and etoposide	Modest anti-tumor effect with a tumor growth delay of 4 days
	Group 3	huN901-DM1 and cisplatin and etoposide	Tumor growth delay of 12 days (50% longer than what one would expect for an additive anti-tumor effect)
Example 4	Control	Phosphate buffered saline	Tumor grew rapidly to about 1000 mm^3 in 26 days
	Group 1	Docetaxel	Tumor growth delay of 8 days
	Group 2	huN901-DM1	Tumor growth delay of 20 days
	Group 3	Docetaxel and huN901-DM1	Complete tumor regression in all animals. In 3 out of 6 animals tumor was eradicated resulting in cures lasting greater than 200 days. In remaining 3 animals, tumor growth delay of 52 days (24 days longer than calculated additive effect).
Example 5	Control	Phosphate-buffered saline	Tumors grew to about 800 mm^3 in 44 days
	Group 1	Topotecan	Tumor growth delays of 12 days
	Group 2	huN901-DM1	Tumor growth delay of 34 days in 3out of 6 animals. Remaining 3 animals had complete tumor regression
	Group 3	Topotecan and huN901-DM1	Complete tumor regression in 5 out of 6 animals and tumor-free on day 78

[4] Office Action at page 9, lines 13-15 and page 11, lines 9-12

Example 6	Control	Phosphate-buffered saline	Tumors grew rapidly to about 1000 mm^3 in 32 days
	Group 1	Paclitaxel	Tumor growth delay of 4 days
	Group 2	huC242-DM1	Shrinkage of tumor, but none of the 6 treated animals showed complete tumor regression
	Group 3	Paclitaxel and huC242-DM1	Showed greater anti-tumor effect resulting in complete tumor regression, with 3 out of 6 animals showing no evidence of tumor. The remaining 3 animals showed significant shrinkage in tumor.
Example 7	Control	Phosphate-buffered saline	Tumors grew rapidly to about 1000 mm^3 in 31 days
	Group 1	CPT-11 (i.e., irinotecan)	Tumor growth delay of 6 days
	Group 2	C242-DM1	Delay in tumor growth of 22 days
	Group 3	CPT-11 (i.e., irinotecan) and C242-DM1	Tumor growth delay of 38 days (10 days longer than calculated additive effect)

Applicant respectfully submits that the unexpectedly superior results shown in Examples 2-7 in the specification successfully rebut the obviousness rejection set forth by the Patent Office. As MPEP § 716.02(a) states:

SUPERIORITY OF A PROPERTY SHARED WITH THE PRIOR ART IS EVIDENCE OF NONOBVIOUSNESS

> Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties ... can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow nutsedge weeds in corn and soybean crops was sufficient to overcome the rejection under 35 U.S.C. 103, even though the specification indicated the claimed compound was an average performer on crops other than corn and soybean.). See also *Ex parte A*, 17 USPQ2d 1716 (Bd. Pt. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut *prima facie* obviousness even though there was no evidence that the compound was effective against all bacteria.)

The MPEP states that evidence of unexpectedly superior results is sufficient to obtain patent protection for claims directed to a compound or composition. In other words, a showing

of unexpectedly superior results does not merely confer patentability to the methods of use — it also confers patentability to the compositions.

Applicant respectfully submits that the results in the specification are commensurate in scope with the claimed invention. In support thereof, Applicant submits herewith a Declaration under 37 CFR § 1.132 by Dr. Walter Blättler ("the Blättler Declaration" attached as Exhibit E).

Dr. Blättler has declared that one skilled in the art would have expected that huN901 and huC242 in Examples 2-7 could have been substituted with other monoclonal antibodies that bind antigens expressed by cancer cells and that the same or substantially the same greater than additive results would have been achieved.[5] Dr. Blättler has also declared that one skilled in the art would have expected that one or more of paclitaxel, cisplatin, etoposide, docetaxel, topotecan, and irinotecan in Examples 2-7 could have been substituted with other chemotherapeutic agents and that the same or substantially the same greater than additive results would have been achieved.

Based on the results in Examples 2-7, the teachings in the specification, the knowledge of one skilled in the art (e.g., that the chemotherapeutic agents in Examples 2-7 have the same or similar mode of action as other chemotherapeutic agents and that the monoclonal antibodies in Examples 2-7 have the same or similar mode of action as other monoclonal antibodies), and the Blättler Declaration, one skilled in the art would recognize that the results demonstrated in Examples 2-7 are commensurate in scope with the pending claims.

In view of the above, Applicant respectfully submit that claims are unobvious over the cited references and respectfully request that the rejections under 35 USC § 103 be withdrawn.

To the extent the third obviousness rejection relies on Lynch, Applicant respectfully submits that Lynch is wholly unrelated to the claimed invention. Lynch discloses N901-br, an immunoconjugate comprising N901 and blocked ricin (br). The PTO has not established any relationship between the immunoconjugate in Lynch, which contains blocked ricin, and the presently claimed immunoconjugate, which comprises a maytansinoid.

Ricin is a catalytically active plant toxin that kills cells by attacking ribosomes (Sandvig et al, *The EMBO Journal*, 19:5943-5950 (2000), attached as Exhibit J). Ricin is functionally similar to Siegall's PE40 (*see* Exhibit J at page 2). Ricin is functionally equivalent to blocked

[5] The Blättler Declaration at ¶ 7.

ricin (Lambert et al, *Cancer Res.*, 51(23 Pt 1):6236-6242 (1991)(Abstract), attached as Exhibit K). Maytansine is an antibiotic originally isolated from an African shrub and is chemically an ansamacrolide or polyketide. (Kupchan et al, *J. Am. Chem. Soc.*, 94: 1354-1356 (1972), attached as Exhibit I). Maytansinoids are antimitotic agents that bind to the intracellular protein tubulin and inhibit its polymerization to form microtubules. The claimed maytansinoids are not enzymes (i.e., like blocked ricin) nor do they act catalytically in any other fashion (i.e., like blocked ricin).

Because the basis for the PTO's third rejection based on Lynch is factually incorrect, Lynch does not properly form a basis to reject the present claims. Without Lynch, the PTO has not clearly not established a *prima facie* case of obviousness for the third obviousness rejection. Accordingly, the third rejection under 35 USC § 103 must be withdrawn.

V. Fourth Rejection under 35 USC § 103

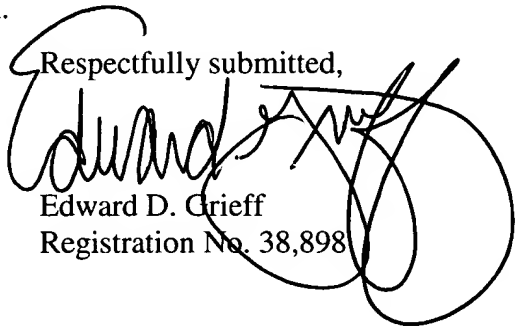
Claims 93-113, and 115-119 are rejected under 35 U.S.C. § 103(a) as being obvious over Guchelaar et al, *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) in view of Liu et al, *Proc Annu Meet Am Assoc Cancer Res*, 38:A190 (1997) and Liu, *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) and Iwasaki et al, *Yakugaku Zasshi*, 118:111-126 (1998) and Pegram et al, *Oncogene*, 18:2241-2251 (1999) and further in view of Schlom, *Molecular Foundations of Oncology*, Ed. S. Broder, pages 95-134 (1991).

Applicant respectfully traverses the rejection. Because claims 93-113, and 115-119 are unobvious over Guchelaar in view of Liu et al, *Proc Annu Meet Am Assoc Cancer Res*, 38:A190 (1997) and Liu, *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) and Iwasaki and Pegram for the reasons discussed in Part IV above (which is incorporated by reference in its entirety), claims 93-113 and 115-119 are also unobvious over Guchelaar in view of Liu et al, *Proc Annu Meet Am Assoc Cancer Res*, 38:A190 (1997) and Liu, *Expert Opinion on Investigational Drugs*, 6:169-172 (1997) and Iwasaki and Pegram and further in view of Schlom. Schlom does not cure the deficiencies of the other references and does not change that the presently claimed invention provides unexpectedly superior results when compared to the prior art. In view thereof, Applicant respectfully requests that this fourth obviousness rejection be withdrawn.

VI. Conclusion

Applicant respectfully requests an early and favorable reconsideration and allowance of pending claims 93-120 and 144-151. The Examiner is encouraged to telephone the undersigned to expedite prosecution of this application.

Respectfully submitted,



Edward D. Grieff
Registration No. 38,898

Date: May 5, 2004
HALE AND DORR LLP
1455 Pennsylvania Avenue, NW
Washington, DC 20004
Phone: 202-942-8400
Fax: 202-942-8484

Table of Exhibits

Exhibit	Reference
A	Stern et al, *Cancer Vaccines and Immunotherapy*, pages 1-18 and 195-206, Cambridge University Press (2000)
B	Kast, *Peptide-Based Cancer Vaccines*, pages 1-16, Eurekah.com, (2000)
C	"Monoclonal Antibody Production," A Report of the Committee on Methods of Producing Monoclonal Antibodies, Institute for Laboratory Animal Research, National Research Council, National Academy Press, Washington, DC, 1999
D	U.S. Patent No. 5,242,824
E	Declaration under 37 CFR § 1.132 by Dr. Walter Blättler
F	Friedman et al, *Cancer Research*, 53(2):334-339 (1993)
G	Webster's New Collegiate Dictionary, G&C Merriam Co., page 1174 (1981)
H	Pastan et al, *J. Biol. Chem.*, 264:15157-15160 (1989)
I	Kupchan et al, *J. Am. Chem. Soc.*, 94: 1354-1356 (1972)
J	Sandvig et al, *The EMBO Journal*, 19:5943-5950 (2000)
K	Lambert et al, *Cancer Res.*, 51(23 Pt 1):6236-6242 (1991)(Abstract)